Original Article

Multimodal Evaluation of Cardiac Myosin Inhibitor Response in Obstructive Hypertrophic Cardiomyopathy Using Echocardiography and Cardiopulmonary Exercise Testing: A Meta-Analysis A Meta-Analysis

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Abstract

Background: **Cardiac Myosin Inhibitors (CMIs), including mavacamten and aficamten, represent a novel class of targeted therapies for obstructive Hypertrophic Cardiomyopathy (oHCM). Their effects on echocardiographic parameters and cardiopulmonary performance across Randomized Controlled Trials (RCTs) have not yet been systematically synthesized.**

Objectives: **To conduct a systematic review and meta-analysis of RCTs in accordance with the PRISMA guidelines.**

Methods: **Primary echocardiographic outcomes included Left Ventricular Ejection Fraction (LVEF), Left Ventricular Mass Index (LVMI), Interventricular Septal Thickness (IVST), E/e' septal ratio, and resting, Valsalva, and post-exercise Left Ventricular Outflow Tract gradients (LVOT-G). Cardiopulmonary Exercise Testing (CPET) outcomes were also assessed. Data were pooled using random-effects models and reported as Mean Differences (MDs) or Standardized Mean Differences (SMDs), with 95% Confidence Intervals (CIs).**

Results: **Five RCTs comprising 767 participants were included. CMIs significantly reduced resting LVOT-G (MD: -37.59 mmHg), Valsalva gradients (MD: -46.45 mmHg), and post-exercise gradients (MD: -49.45 mmHg; all $p < 0.01$). Reverse cardiac remodeling was reflected by reductions in LVMI (MD: -11.96 g/m²), IVST (SMD: -0.98), and E/e' septal ratio (MD: -3.53), along with an expected modest reduction in LVEF (MD: -4.33%). CPET outcomes also improved significantly, including ventilatory efficiency (MD: –2.25), peak metabolic equivalents (METs) (MD: +0.45), peak circulatory power (MD: +482.78 mL/kg/min × mmHg), and exercise duration (MD: +0.88 min; all $p < 0.01$). Subgroup analyses revealed no significant differences between the agents.**

Conclusion: **CMIs promote reverse cardiac remodeling, improve hemodynamics, and enhance exercise tolerance in patients with oHCM, supporting their role as disease-modifying targeted therapies.**

Keywords: **Hypertrophic Cardiomyopathy; Echocardiography; Meta-Analysis.**

Introduction

Obstructive Hypertrophic Cardiomyopathy (oHCM) is a prevalent form of hypertrophic cardiomyopathy characterized by asymmetric septal hypertrophy and dynamic Left Ventricular Outflow Tract Obstruction (LVOTO).[1,2] This condition leads to symptoms such as exertional dyspnea, chest pain, fatigue, and syncope, often resulting in reduced functional capacity and increased morbidity.[3,4]

Traditional pharmacological therapies — including beta-blockers, calcium channel blockers, and disopyramide — aim to alleviate symptoms by reducing contractility and LVOTO. However, their effects on disease progression and structural remodeling remain limited. Recently, Cardiac Myosin Inhibitors (CMIs), including mavacamten and aficamten, have emerged as targeted therapies capable of directly modulating sarcomeric function.[5–7] Early clinical trials suggest that these agents improve hemodynamic parameters, relieve LVOT obstruction, and favorably affect cardiac structure and exercise capacity.

Cardiopulmonary exercise testing (CPET) plays a central role in assessing functional capacity in patients with oHCM by providing objective measures such as peak oxygen consumption (VO_2peak) and ventilatory efficiency, both of which closely correlate with symptom burden and exercise tolerance.[8,9] Similarly, echocardiographic parameters — including septal thickness, left atrial volume, and LVEF — serve as key indicators of myocardial structure and function.[10,11] Although early studies suggest that CMIs improve these parameters, the magnitude and consistency of these effects across randomized clinical trials remain to be fully established.[12–14]

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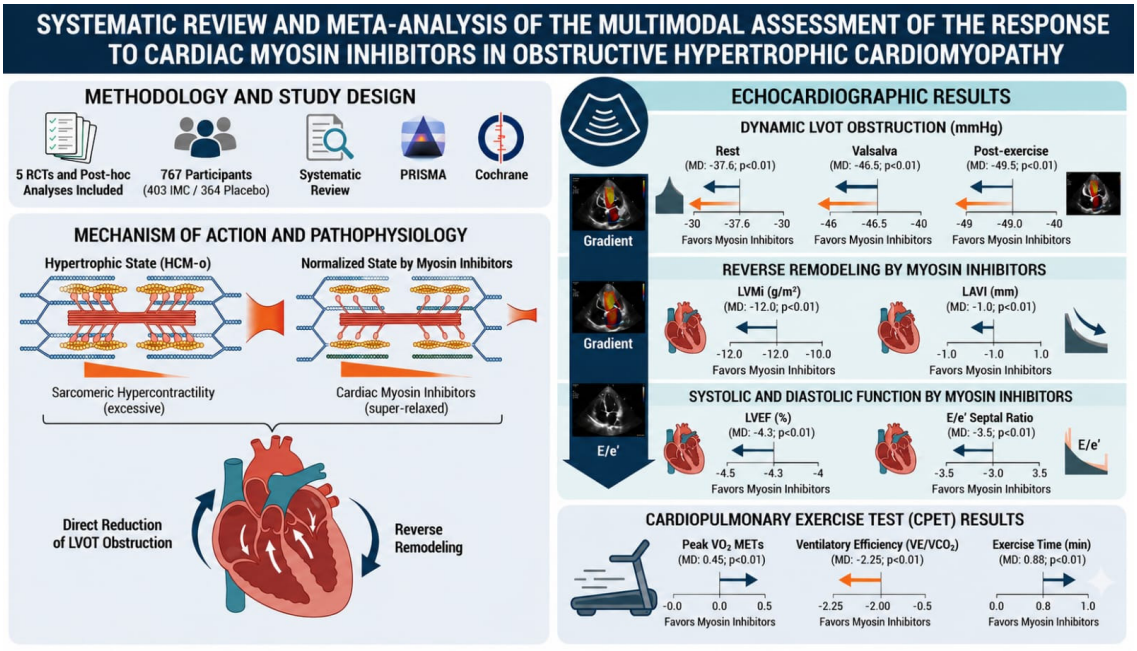
Manuscript received May 25, 2026, revised manuscript June 10, 2026, accepted July 5, 2026
Editor responsible for the review: Maria Otto

DOI: https://doi.org/10.36660/abcimg.2026007i

Central Illustration: Multimodal Evaluation of Cardiac Myosin Inhibitor Response in Obstructive Hypertrophic Cardiomyopathy Using Echocardiography and Cardiopulmonary Exercise Testing: A Meta-Analysis A Meta-Analysis



Arq Bras Cardiol: Imagem cardiovasc. 2026;39(3):e20260077

RCTs: Randomized Clinical Trials; CMIs: Cardiac Myosin Inhibitors; CPET: Cardiopulmonary Exercise Testing; oHCM: Obstructive Hypertrophic Cardiomyopathy.

This systematic review and meta-analysis aimed to synthesize evidence from randomized controlled trials (RCTs) evaluating the effects of CMIs on echocardiographic markers of left ventricular structure and function, as well as CPET outcomes, in patients with oHCM.

Methods

Protocol and Registration

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[15,16] The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251078060.

Eligibility Criteria

We included RCTs and pre-specified or clearly identified post hoc analyses derived from RCTs that evaluated the effects of CMIs compared with placebo on CPET outcomes and left ventricular structure and function in patients with oHCM. No restrictions were applied regarding publication date, language, or geographic location. Studies were excluded if they contained incomplete or unavailable data, were conference abstracts, letters, expert opinions, case reports, review articles, duplicate publications, studies involving untreated patients, or animal studies.

Search Strategy and Study Selection

A systematic literature search was conducted in May 2025 using Cochrane CENTRAL, PubMed, and Embase. The search strategy included terms related to CMIs and oHCM (detailed in Supplementary Table 1). Study selection was performed in two stages using Rayyan. Titles and abstracts were screened first, followed by full-text assessment of potentially eligible studies. Both stages were conducted independently by two reviewers, with disagreements resolved by consensus or by consultation with a third reviewer.

Outcomes

CPET outcomes included ventilatory efficiency (minute ventilation [VE]/carbon dioxide output [VCO_2] slope during exercise), peak circulatory power (peak VO_2 × peak systolic blood pressure), peak metabolic equivalents (METs), and exercise duration. Left ventricular structure and function outcomes included changes from baseline in resting, Valsalva, and post-exercise left ventricular outflow tract gradients (LVOT-G), left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), interventricular septal thickness (IVST), and E/e' septal ratio. Subgroup analyses stratified according to study drug (mavacamten or aficamten) were performed whenever feasible.

Two investigators independently extracted the data into Microsoft Excel spreadsheets, followed by cross-checking of the extracted information.

Quality and Risk of Bias Assessment

The risk of bias of the included RCTs and eligible post hoc analyses derived from these trials was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool for the specific outcomes of interest.[17] For post hoc analyses, particular attention was paid to the pre-specification of outcomes and the potential for selective outcome reporting. Disagreements between reviewers were resolved through discussion or, when necessary, by consultation with a third reviewer. Given the limited number of included studies, publication bias was not formally assessed.

Statistical Analysis

Continuous outcomes were analyzed using Mean Differences (MDs) with corresponding 95% confidence intervals (CIs). Heterogeneity was assessed using restricted maximum likelihood (REML) estimation and the I^2 statistic, with $p < 0.05$ or $I^2 > 50\%$ considered indicative of substantial heterogeneity. Pooled analyses were performed using both the inverse-variance common-effect model and the DerSimonian–Laird random-effects model, with statistical significance defined as $p < 0.05$. Forest plots were generated to illustrate individual study estimates and pooled effect sizes. Meta-analyses were performed using RStudio (version 2023.12.1+402) and the meta package for data synthesis and visualization.

Results

Search Results

A total of 1,448 records were identified through database searching. After screening and eligibility assessment, five RCTs met the inclusion criteria, and their post hoc analyses were incorporated into the meta-analysis (Figure 1).[18–27]

Study and Participant Characteristics

The included studies comprised a total of 767 participants, with 403 assigned to the CMI group and 364 to the placebo group (Central Illustration). All trials were published between 2020 and 2024, and their main characteristics are summarized in Table 1.

LVEF

LVEF was significantly reduced with CMIs (MD: -4.33%; 95% CI: -5.33 to -3.33; $p < 0.01$; $I^2 = 0\%$), as shown in Figure 2A. Aficamten was associated with a slightly greater reduction (-5.00; 95% CI: -6.50 to -3.50) than mavacamten (-3.80; 95% CI: -5.14 to -2.47), although the subgroup difference was not statistically significant ($p = 0.24$).

LVMI

A significant reduction in LVMI was observed in patients treated with CMIs compared with placebo (MD: -11.96 g/m^2; 95% CI: -17.72 to –6.19; $p < 0.01$; $I^2 = 68.1\%$; Figure 2B). Subgroup analysis showed similar effects for aficamten (MD: -12.20; 95% CI: -17.95 to -6.45) and mavacamten (MD: -11.49; 95% CI: -21.56 to -1.42), with no significant difference between groups ($p = 0.90$).

IVST

CMIs were associated with a moderate reduction in IVST (SMD: -0.98; 95% CI: -1.51 to -0.46; $p < 0.01$; $I^2 = 48.3\%$; Figure 3A). Aficamten (SMD: -1.00; 95% CI: -1.65 to -0.35) and mavacamten (SMD: -0.85; 95% CI: -1.91 to 0.22) showed no significant subgroup differences ($p = 0.81$).

E/e' Septal Ratio

A significant reduction in the E/e' septal ratio was observed (MD: -3.53; 95% CI: -4.35 to -2.71; $p < 0.01$; $I^2 = 0\%$; Figure 3B). Aficamten (-3.60; 95% CI: -4.75 to -2.45) and mavacamten (-3.45; 95% CI: -4.62 to -2.28) yielded comparable results ($p = 0.86$).

Resting LVOT-G

CMIs significantly reduced resting LVOT-G (MD: -37.59 mm Hg; 95% CI: -47.35 to -27.83; $p < 0.01$; $I^2 = 62.9\%$; Figure 4A). Sensitivity analysis (Supplementary Figure 1) confirmed the robustness of this finding, with pooled MDs ranging from -35.10 to -39.83 mm Hg across all leave-one-out iterations. Heterogeneity varied from low to moderate ($I^2 = 23.5\%$ to 71.1%), indicating that no individual study disproportionately influenced the overall effect estimate.

Valsalva LVOT-G

CMIs were associated with a significant pooled reduction in Valsalva LVOT-G (MD: -46.45 mm Hg; 95% CI: -60.86 to -32.05; $p < 0.01$; $I^2 = 76.6\%$; Figure 4B). Aficamten reduced the gradient by -40.05 mm Hg (95% CI: -60.79 to -19.31), whereas mavacamten reduced it by -51.83 mm Hg (95% CI: -75.49 to -28.17), with no significant difference between subgroups ($p = 0.46$). Leave-one-out analysis confirmed the robustness of the findings (Supplementary Figure 2), with pooled effect estimates ranging from -41.39 to -50.43 mm Hg. Heterogeneity remained moderate to high ($I^2 = 50.3\%$ to 83.4%) across all iterations.

Post-Exercise LVOT-G

CMIs were associated with significantly lower post-exercise LVOT-G (MD: -49.45 mm Hg; 95% CI: -74.93 to -23.98; $p < 0.01$; $I^2 = 84.6\%$; Figure 4C). Leave-one-out analysis confirmed the robustness of these findings (Supplementary Figure 3), with pooled effect estimates ranging from -56.99 to -37.10 mm Hg. Heterogeneity decreased substantially ($I^2 = 0\%$) after exclusion of the EXPLORER-CN study.

Ventilatory Efficiency

CMIs significantly improved ventilatory efficiency compared with placebo (MD: -2.25; 95% CI: -2.87 to -1.63; $p < 0.01$; $I^2 = 0\%$), as shown in Figure 5A.

Peak Circulatory Power

CMIs significantly increased peak circulatory power (MD: 482.78 mL/kg/min × mm Hg; 95% CI: 274.05 to 691.51; $p < 0.01$; $I^2 = 47.7\%$; Figure 5B).

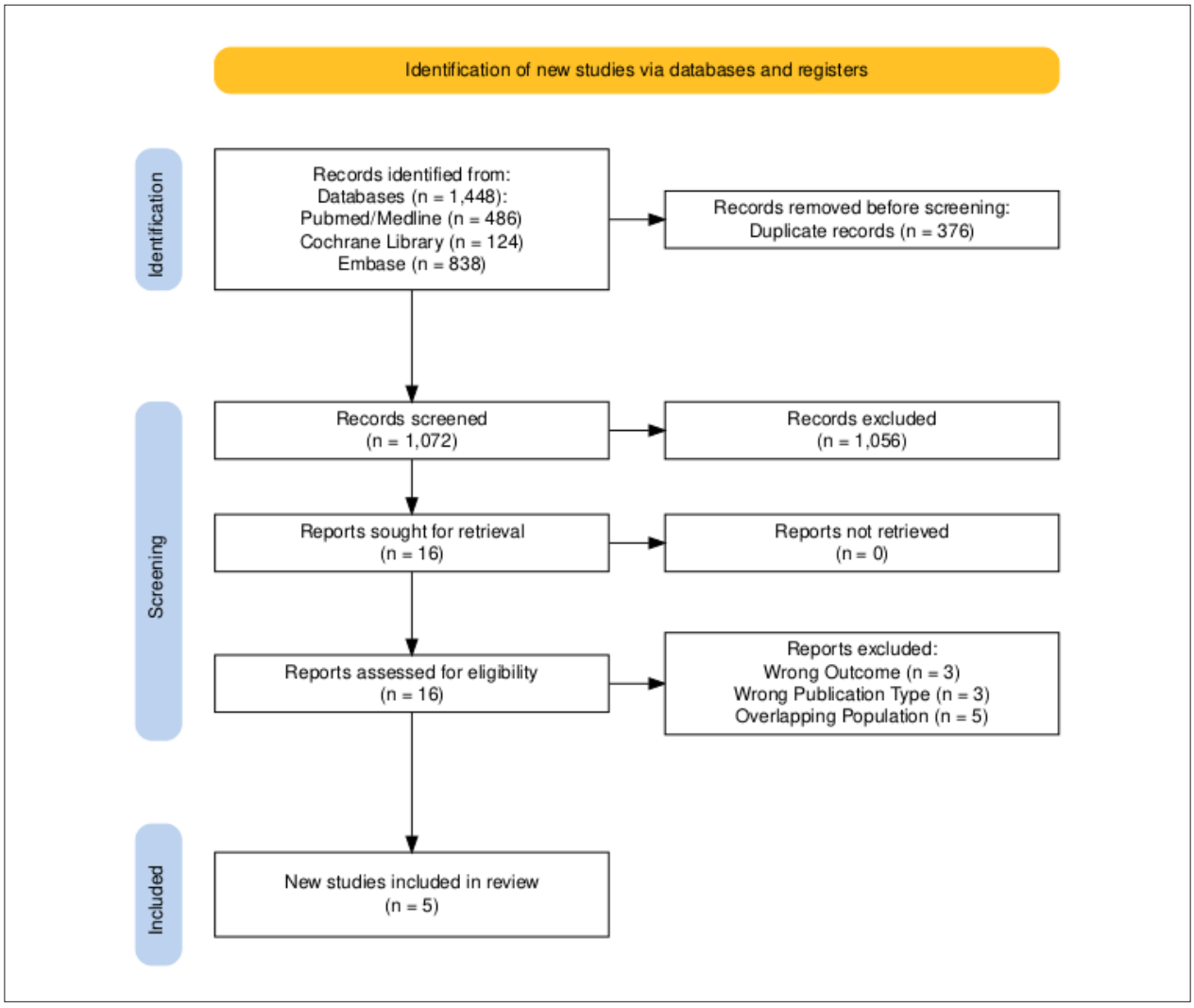


Figure 1 – *PRISMA flow diagram of the systematic review and meta-analysis.*

Tabela 1 – Características dos estudos incluídos e dados demográficos basais

Study	Number of Participants		Males, %		Age, years†		NYHA functional class II vs III, %		LVEF, %†		*LVOT-G at rest*, mm Hg†	
	CMI	Placebo	CMI	Placebo	CMI	Placebo	CMI	Placebo	CMI	Placebo	CMI	Placebo
EXPLORER-HCM	123	128	54	65	58.5	58.5	72 vs 28	74 vs 26	74	74	52	51
EXPLORER-CN	54	27	75.9	63.0	52.4	51.0	82 vs 18	67 vs 33	77.8	77.0	–	–
VALOR-HCM	56	56	51.8	50.0	59.8	60.9	7 vs 93	7 vs 93	67.9	68.3	51.2	46.3
REDWOOD-HCM	28	13	46	38	57	59	61 vs 39	85 vs 15	70††	75††	53††	71††
SEQUOIA-HCM	142	140	60.6	57.9	59.2	59.0	76 vs 24	76 vs 24	74.8	74.8	54.8	55.3

†Mean; ††Median; CMI: Cardiac myosin inhibitor; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; LVOT-G: left ventricular outflow tract gradient.

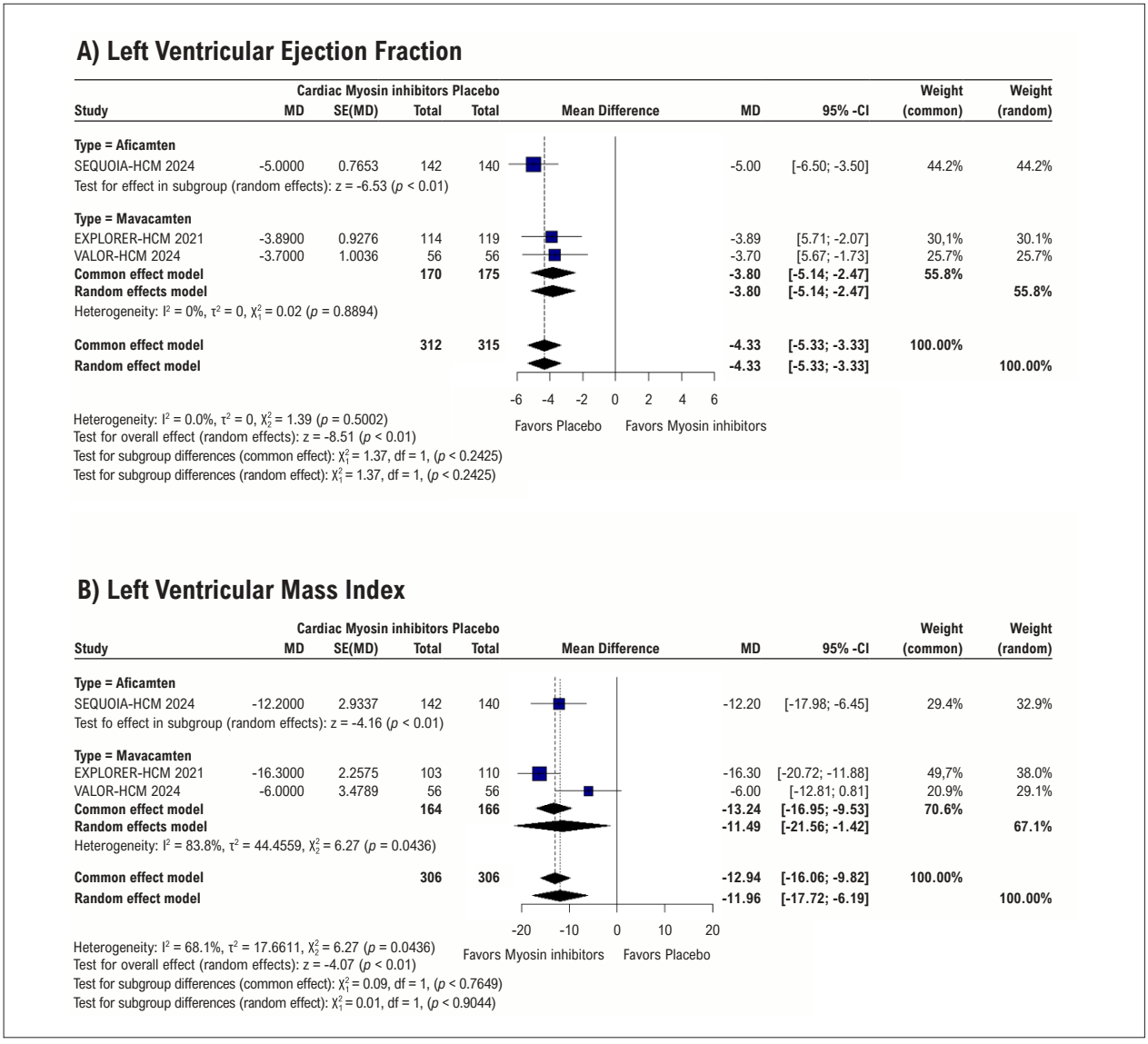


Figure 2 – *Meta-Analysis of Left Ventricular Structural Outcomes. Results of the meta-analysis for (A) LVEF and (B) LVMI, comparing CMIs (aficamten and mavacamten) with placebo. Boxes are proportional to the weight of each study, and horizontal lines represent the corresponding 95% CIs. Diamonds represent the pooled MDs for each subgroup and the overall analysis, with diamond width corresponding to the 95% CI. Values to the left of the vertical line of no effect indicate reductions in these parameters, favoring treatment with CMIs. SE: Standard Error; MD: Mean Differences; CI: confidence intervals.*

Peak METs

CMIs significantly increased peak METs (MD: 0.45 METs; 95% CI: 0.30 to 0.60; $p < 0.01$; $I^2 = 0\%$; Figure 5C).

Exercise Duration

Exercise duration was significantly longer in patients treated with CMIs (MD: 0.88 min; 95% CI: 0.53 to 1.24; $p < 0.01$; $I^2 = 0\%$; Figure 5D).

Risk of Bias Assessment

All included studies were judged to be at low risk of bias across all five domains assessed. Accordingly, the overall risk of bias was considered low for all studies. A detailed visual summary of the risk-of-bias assessment is provided in Supplementary Figure 4.

Discussion

This meta-analysis synthesizes high-quality evidence from RCTs demonstrating that CMIs — namely mavacamten and aficamten — significantly improve cardiopulmonary performance and cardiac structural parameters in patients with oHCM. These findings support the disease-modifying potential of CMIs by directly targeting sarcomeric hypercontractility, a central pathophysiological mechanism in hypertrophic cardiomyopathy, rather than relying solely on negative chronotropic or vasodilatory effects.

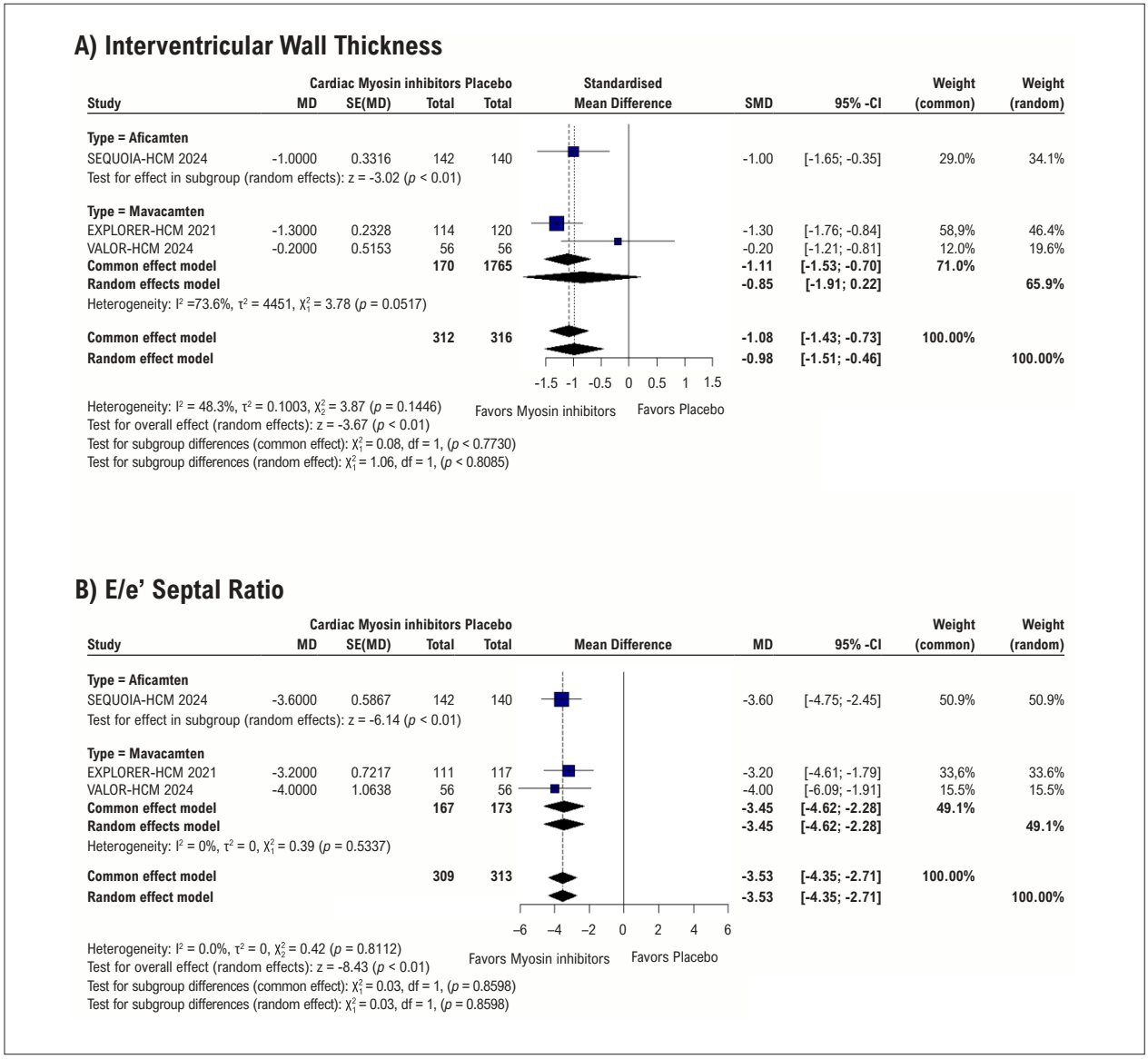


Figure 3 – *Meta-Analysis of Interventricular Septal Structural Outcomes. Results of the meta-analysis for (A) IVST and (B) E/e' septal ratio, comparing CMIs (aficamten and mavacamten) with placebo. Values to the left of the vertical line of no effect indicate reductions in IVST and E/e' septal ratio, favoring treatment with CMIs. SMD: Standardized Mean Differences; MD: Mean Differences; CI: confidence intervals; HCM: Hypertrophic Cardiomyopathy; SE: Standard Error.*

The molecular basis of oHCM is primarily driven by pathogenic sarcomeric variants — most commonly involving MYH7 and MYBPC3 — that increase the proportion of myosin heads in the Disordered Relaxed (DRX) state, leading to excessive actin–myosin cross-bridge cycling, increased myocardial ATPase activity, and augmented contractile force even at submaximal calcium concentrations.[28,29] This hypercontractile phenotype contributes not only to resting and provoked LVOT-G but also to chronically increased wall stress, myocyte disarray, and maladaptive hypertrophic remodeling, particularly involving the basal interventricular septum.[1,30]

CMIs bind allosterically to the catalytic domain of β-cardiac myosin, reducing the availability of myosin heads in the DRX state while promoting the super-relaxed state.[31,32] This mechanism stabilizes sarcomeric energetics and directly attenuates contractile force without affecting calcium cycling.[33] Unlike conventional therapies, such as β-blockers and disopyramide, which reduce contractility indirectly through adrenergic or ionotropic modulation and may compromise systemic hemodynamics, CMIs act directly on the underlying molecular mechanism of disease.[34,35]

The marked reductions in LVOT-G observed at rest, during the Valsalva maneuver, and after exercise demonstrate effective attenuation of the dynamic obstruction responsible for the hemodynamic burden of oHCM. The magnitude of gradient reduction (e.g., -37.6 mm Hg at rest and -46.5 mm Hg during the Valsalva maneuver) is comparable to that reported following

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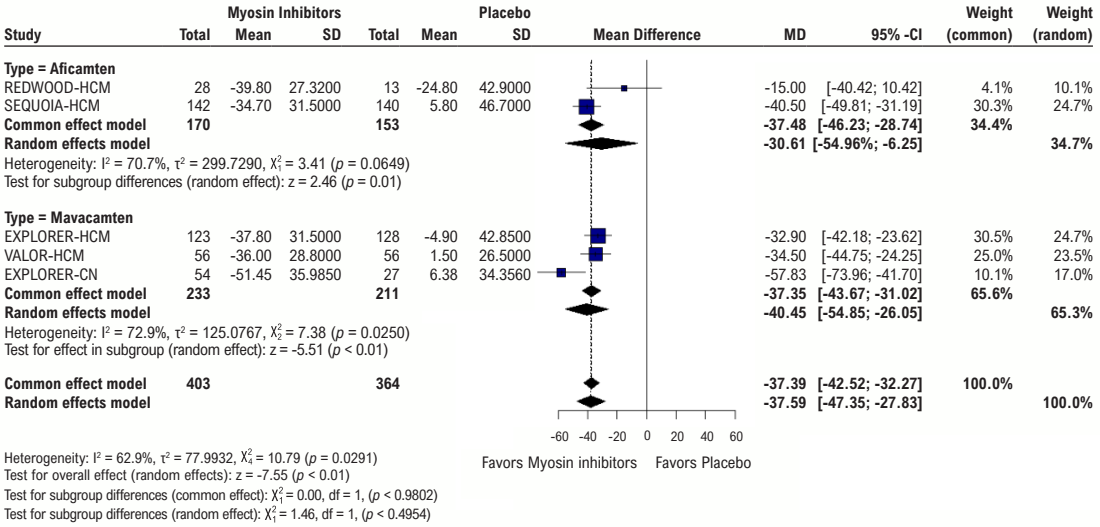
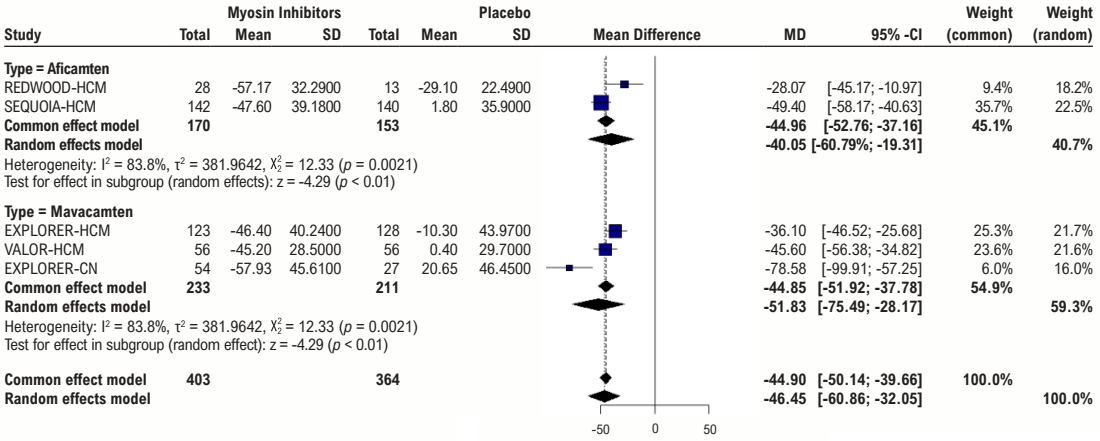
A) Resting Left Ventricular Outflow Tract Gradient



Heterogeneity: I^2 = 62.9%, τ^2 = 77.9932, X^2_4 = 10.79 (p = 0.0291)
Test for overall effect (random effects): z = -7.55 (p < 0.01)
Test for subgroup differences (common effect): X^2_1 = 0.00, df = 1, (p < 0.9802)
Test for subgroup differences (random effect): X^2_1 = 1.46, df = 1, (p < 0.4954)

B) Valsalva Left Ventricular Outflow Tract Gradient



Heterogeneity: I^2 = 76.6%, τ^2 = 220.1691, X^2_4 = 17.06 (p = 0.0019)
Test for overall effect (random effects): z = -6.32 (p < 0.01)
Test for subgroup differences (common effect): X^2_1 = 0.00, df = 1, (p = 0.9838)
Test for subgroup differences (random effect): X^2_1 = 0.54, df = 1, (p = 0.4631)

C) Post-exercise Left Ventricular Outflow Tract Gradient

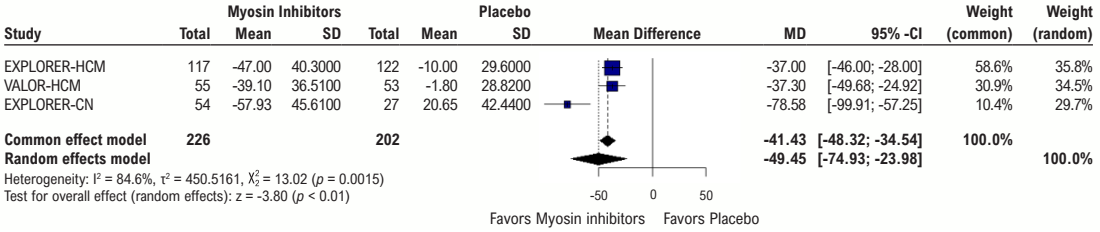


Figure 4 – *Meta-Analysis of LVOT-G Outcomes. Results of the meta-analysis for (A) resting LVOT-G, (B) Valsalva LVOT-G, and (C) post-exercise LVOT-G, comparing CMIs (aficamten and mavacamten) with placebo. Values to the left of the vertical line of no effect indicate lower LVOT-Gs, favoring treatment with CMIs. MD: Mean Differences; CI: confidence intervals; HCM: Hypertrophic Cardiomyopathy; SE: Standard Error.*

septal reduction therapy. Furthermore, the consistency of these effects across different physiological conditions suggests sufficient suppression of basal hypercontractility to mitigate both resting and provocable gradients.[36,37]

Importantly, this gradient reduction translates into enhanced exercise capacity. Peak METs, peak circulatory power, and exercise duration all improved significantly following CMI therapy, with minimal between-study heterogeneity. These CPET parameters reflect integrated cardiovascular performance, encompassing preload reserve, myocardial contractile reserve, chronotropic competence, and peripheral oxygen utilization.[25] Likewise, the improvement in ventilatory efficiency — a surrogate marker of pulmonary vascular coupling and left-sided filling pressures — suggests favorable effects on diastolic function and pulmonary vascular compliance.[38-40]

Beyond their hemodynamic effects, CMIs produced statistically and clinically significant reductions in IVST and LVMI, reinforcing their capacity to promote reverse cardiac remodeling.[41] The reduction in septal thickness supports true structural regression rather than merely transient functional unloading. These structural changes were accompanied by improvements in diastolic function, as evidenced by lower E/e' septal ratios, an echocardiographic marker of reduced left ventricular filling pressures and improved ventricular compliance.[42] Given the well-established association between elevated filling pressures and symptom burden in oHCM, these findings indicate that CMIs favorably affect both the mechanical and diastolic components of the disease.[43]

The modest reduction in LVEF observed with CMI therapy should be interpreted within the appropriate clinical context. Patients with oHCM frequently exhibit supranormal ejection fractions (> 70%), reflecting hypercontractile systolic mechanics rather than increased forward cardiac output.[44] CMIs normalize sarcomeric force generation, reducing LVEF toward the physiological range while preserving stroke volume. Importantly, none of the included studies reported reductions in LVEF below the pathological threshold (< 50%), indicating that this decrease reflects the intended pharmacological effect rather than myocardial dysfunction.[45] Although aficamten was associated with a slightly greater reduction in LVEF than mavacamten, this difference may be explained by its faster onset of action, shorter half-life (approximately 3 vs. 7 days), and lower interindividual pharmacokinetic variability.[46]

Subgroup analyses revealed no significant differences between mavacamten and aficamten across structural and functional outcomes, suggesting a class effect attributable to their shared sarcomeric mechanism of action. Nevertheless, pharmacokinetic differences may influence clinical implementation, particularly with respect to dose titration, echocardiographic monitoring of LVEF, and potential drug–drug interactions.[47,48] Heterogeneity was low to moderate across most analyses. The greater variability observed for Valsalva and post-exercise LVOT-G likely reflects differences in provocation protocols and baseline gradient severity among the included studies. Leave-one-out analyses confirmed the robustness of the pooled estimates, further supporting the internal validity of the findings.

Collectively, these findings reinforce the role of CMIs as upstream modulators of oHCM pathophysiology, offering a pharmacological alternative to septal reduction therapy for patients with persistent gradients and symptomatic limitation despite guideline-directed medical therapy.[49,50] Given their favorable effects on cardiac structure, function, and symptoms, CMIs may also hold promise as preventive therapy in genotype-positive individuals at high risk or in patients with early phenotypic expression, although this hypothesis remains investigational.[51] In addition, CMIs may represent an attractive therapeutic option for patients who are ineligible for or unwilling to undergo septal myectomy or alcohol septal ablation.[52] Nevertheless, because of the potential for excessive LVEF reduction, careful echocardiographic monitoring remains essential during dose titration.

Several limitations should be acknowledged. First, the number of included RCTs was relatively small, and follow-up periods were short, precluding conclusions regarding long-term outcomes such as heart failure progression, atrial fibrillation, or sudden cardiac death. Second, most studies excluded patients with advanced NYHA functional class, mid-ventricular obstruction, or apical variants, limiting the generalizability of these findings. Future studies should evaluate myocardial fibrosis and extracellular volume, incorporate genotype-stratified analyses, and investigate synergistic therapeutic strategies, including combinations of CMIs with RAAS inhibitors or antifibrotic agents. Finally, long-term registries will be essential to establish the long-term safety, cost-effectiveness, and durability of treatment response.

Conclusion

CMIs significantly improve functional capacity and promote favorable cardiac remodeling in patients with oHCM by directly targeting sarcomeric hypercontractility, the central mechanism underlying LVOTO and myocardial hypertrophy. This meta-analysis demonstrates that mavacamten and aficamten reduce LVOT-G, improve diastolic function, and enhance exercise capacity, with consistent effects across both agents. These findings support the incorporation of CMIs as disease-modifying therapy for oHCM, although additional studies are warranted to establish their long-term clinical benefits and broader applicability.

Author Contributions

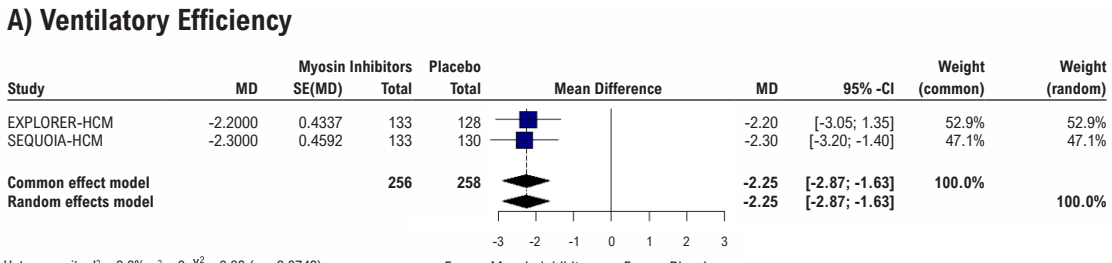
Conception and design of the research, acquisition of data, and statistical analysis: Ramos JVO; analysis and interpretation of the data: Ramos JVO, Fernandes JVA; writing of the manuscript: Ramos JVO, Fernandes JVA, Fernandes LHC, Figueiredo VLFA, Estrela JVO; critical revision of the manuscript for intellectual content: Ramos JVO, Fernandes JVA, Fernandes LHC, Figueiredo VLFA, Estrela JVO, Tavares M; project administration and supervision: Tavares M.

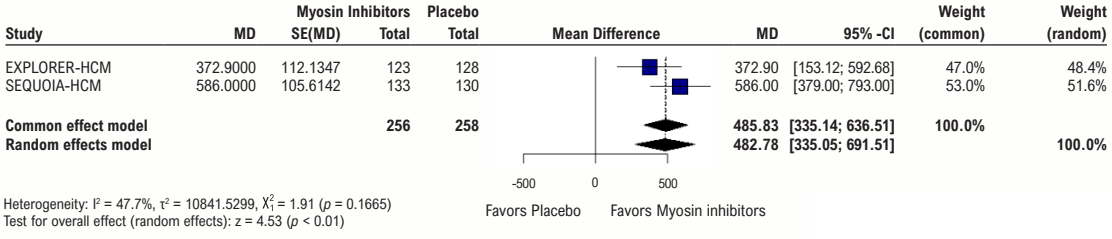
Potential Conflict of Interest

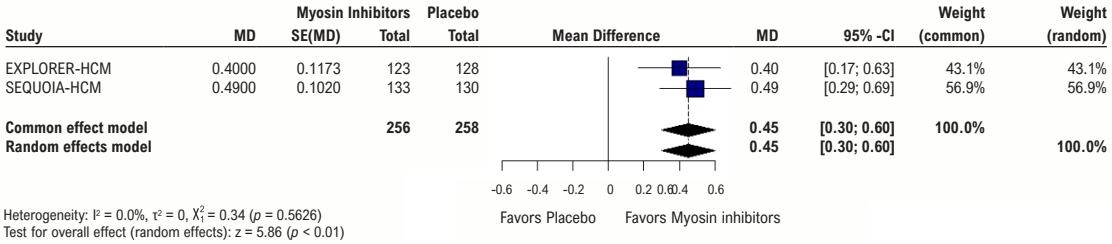
No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.







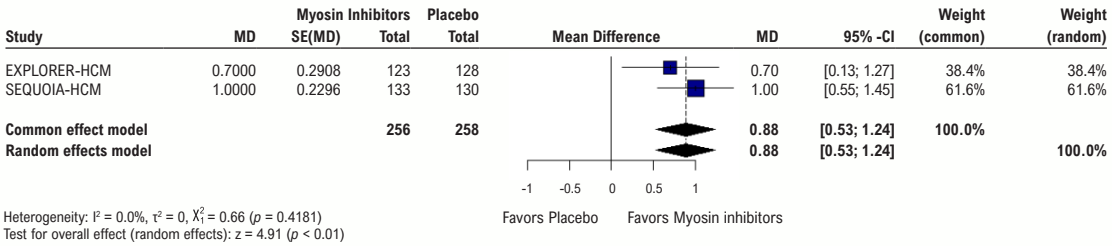


Figure 5 – *Meta-Analysis of CPET Outcomes. Results of the meta-analysis for (A) ventilatory efficiency, (B) peak circulatory power, (C) peak METs, and (D) exercise duration, comparing CMIs with placebo. MD: Mean Differences; CI: confidence intervals; HCM: Hypertrophic Cardiomyopathy; SE: Standard Error.*

Study Association

This study is not associated with any thesis or dissertation work.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Availability of Research Data

The underlying content of the research is contained within the manuscript.

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***Supplemental Materials**

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